MAFF
Ministry of Agriculture, Forestry and Fisheries
農林水産省

Legal framework for the approval/designation of alternatives to antibiotics

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Topics

- National Action Plan on Antimicrobial Resistance (AMR) in Japan
- Approval of Veterinary Medicinal Products (VMPs)
- Designation of Feed Additives
- Promotion of R&D on Alternatives to antimicrobials

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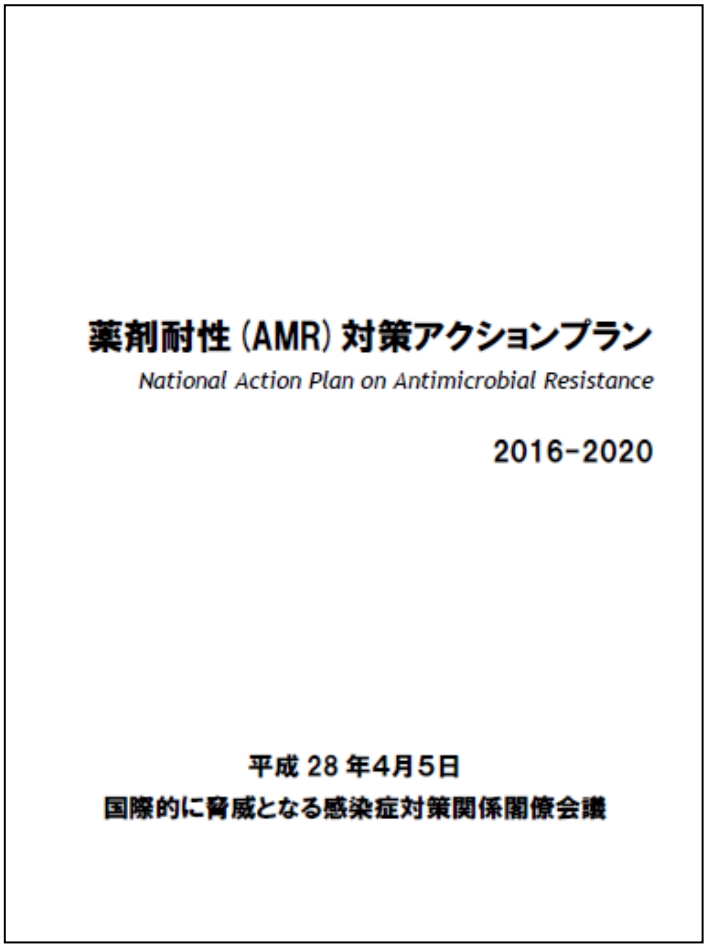
Adoption of AMR National Action Plan, April 5, 2016

Ministerial Council on the Response to Infectious Diseases that Pose a Threat to Global Society

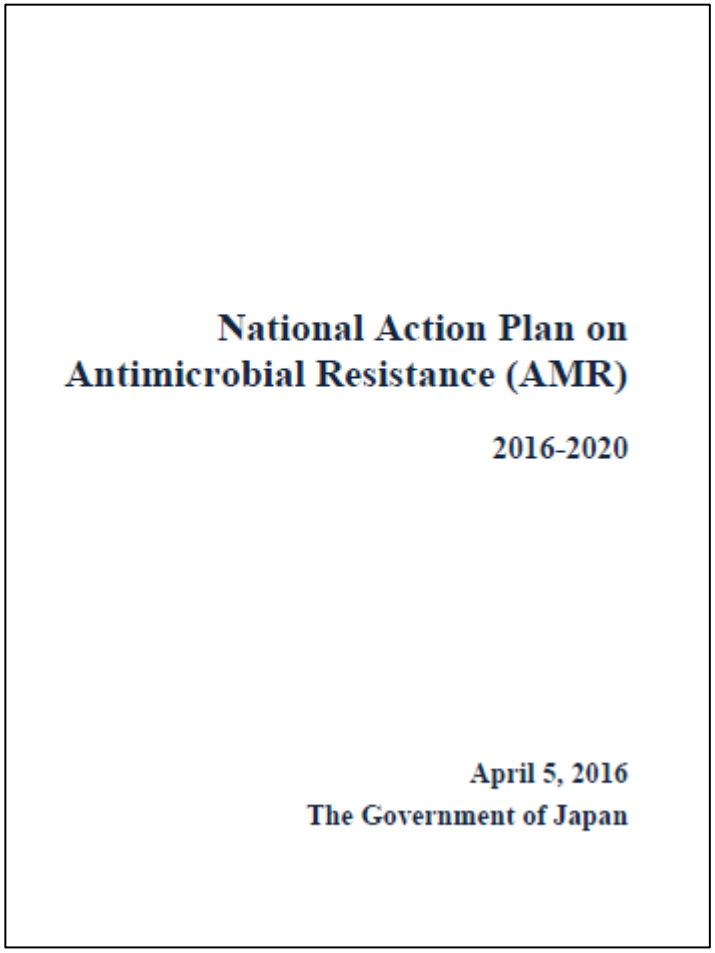
Prime Minister Shinzo Abe:

- AMR is a global threat and Japan has determined our first action plan.
- We will advance effective measures for **both humans and animals**.
- Japan will lead the advancement of international measures such as by **supporting the formulation of action plans in other countries**.
- I request that **all relevant ministers collaborate closely** to steadily advance the relevant measures.

Japan’s national action plan



Japanese version



English version

The outline of National Action Plan on AMR

Goal	Point of actions in animal sector
1. Awareness and education	・Raise awareness of stakeholders including livestock producers
2. Surveillance and monitoring	・Further promote collaboration between human health and animal health sectors ・Expand the scope/target of monitoring and surveillance in aquaculture ・Establish a monitoring and surveillance system for companion animals
3. Infection prevention and control	・Ensure compliance of the Standards of Rearing Hygiene Management
4. Appropriate use of antimicrobials	・Thoroughly implement risk management measures based on risk assessments ・Further promote prudent use of antimicrobials
5. **Research and development**	・**Promote R&D of alternatives to antimicrobials including vaccines**
6. International cooperation	・Contribution to the Asian Region

Budget for the Industry/Academia on VMPs [FY 2019, within 70 million JPY]

To promote
1) fast approval of safe and efficacious VMPs;
2) developments of VMPs for minor use/minor species;
3) **developments of products required for combatting AMR**.

<Menu>

1. Developments of international harmonized technical guidelines

VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products)

2. Developments of national technical guidelines for products using new technology

Support to develop national guidelines for brand new products

3. Developments of products using new technology

Support to obtain data for dossier of products using new technology (e.g., GMO vaccines) at the final stage of R&D (e.g., efficacy studies, safety studies, clinical trials)

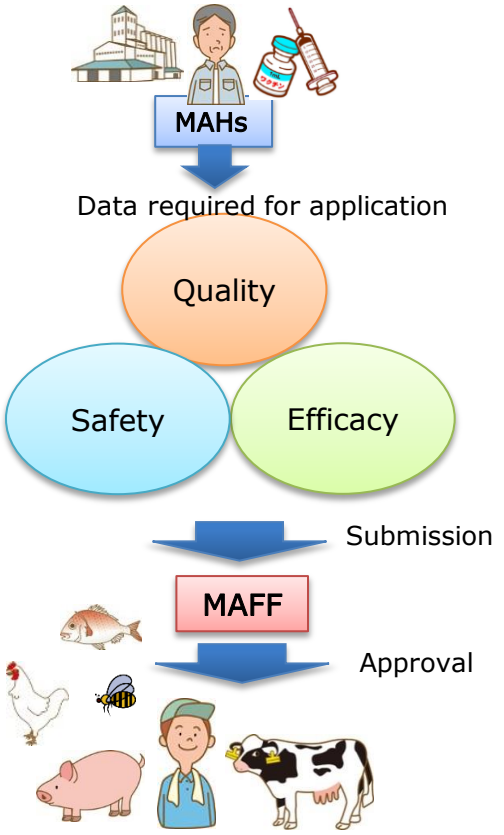
4. Developments of products for minor use/minor species

Support to obtain data for dossier of products for MUMS at the final stage of R&D (e.g., efficacy studies, safety studies, clinical trials)

5. Developments of products for combatting AMR

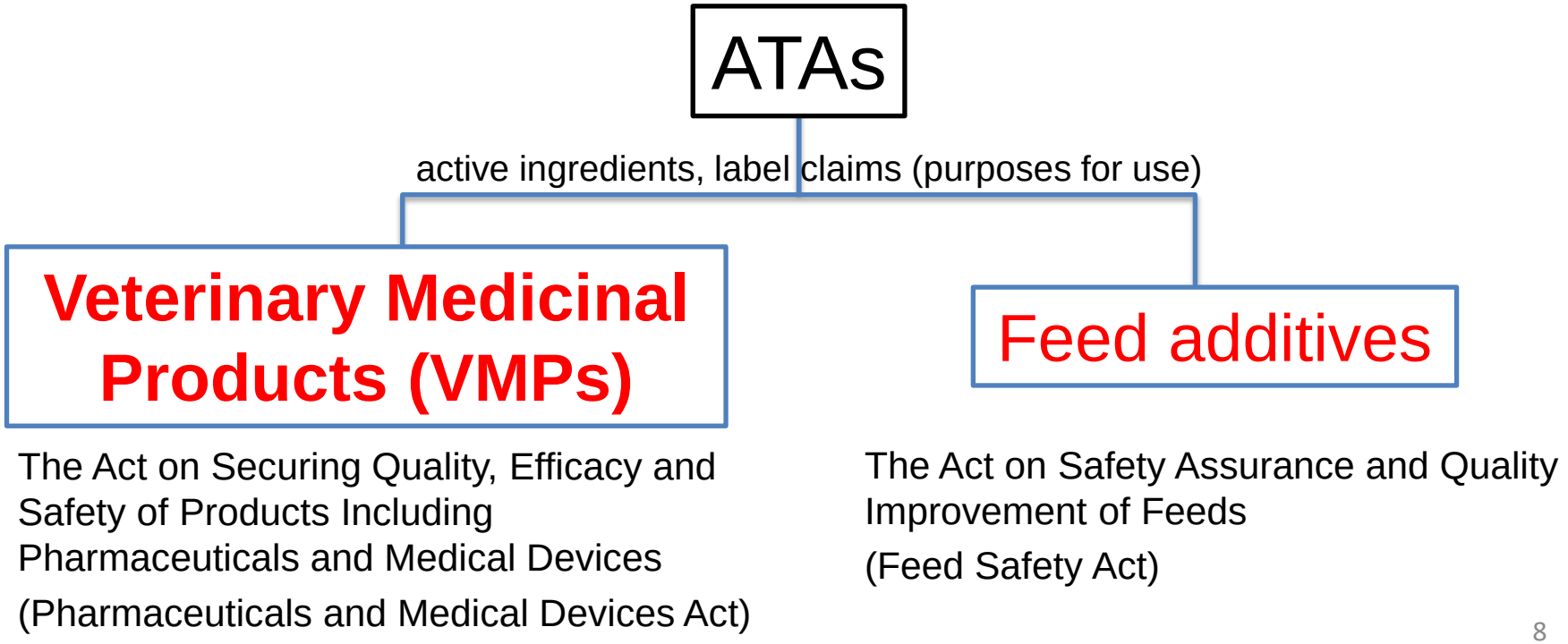
Support to obtain data for dossier of products for combatting AMR (e.g., Alternatives to antibiotics including vaccines) at the final stage of R&D (e.g., efficacy studies, safety studies, clinical trials)

<Image of the project>



Alternatives to antibiotics (ATAs)

- ATAs include, but are not limited to, vaccines, cytokines, enzymes, immunomodulators, immunostimulants, organic acids, probiotics, herbal medicines and bacteriophages.



Topics

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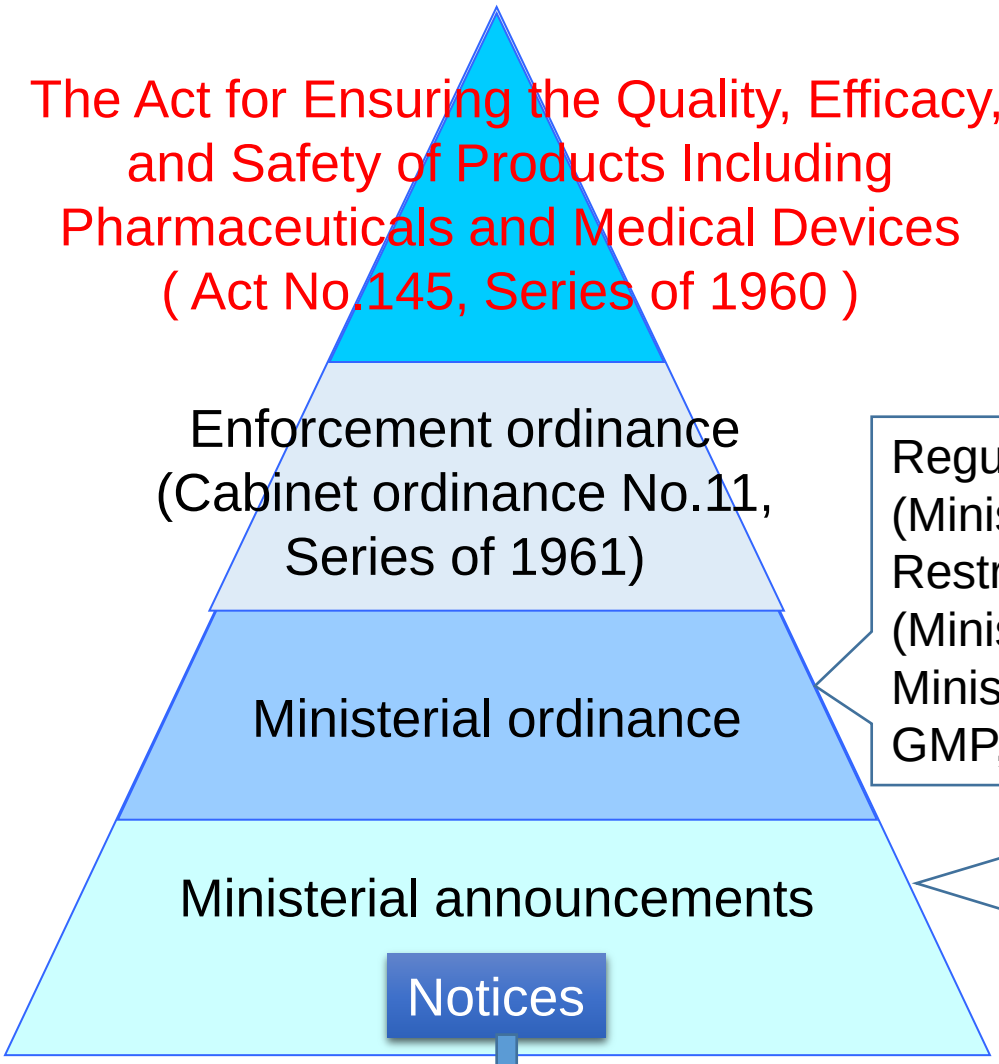
- Promotion of R&D on Alternatives to antimicrobials

Law hierarchy of Pharmaceutical Affairs in Japan



They cover veterinary medicinal products (VMPs) for all animal species

Regulatory rules for Veterinary Products (Ministerial ordinance No. 107, Series of 2004)
Restriction for the usage of VMPs and MPs (Ministerial ordinance No. 44, Series of 2013)
Ministerial Ordinances concerning GLP, GCP, GMP, etc.

Biological products standard,

National testing standard, etc.

National/International (VICH) guidelines

Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act)

Article 1 (Purpose of the Act)

- The purpose of this Act is to improve health and hygiene by providing the control required for securing the quality, efficacy and safety of pharmaceuticals, quasi-pharmaceutical products, cosmetics, medical devices, regenerative medicine products (hereinafter referred to as "pharmaceuticals, etc.") and for preventing the occurrence or spread of health and hygiene-related hazards caused by the use of those pharmaceuticals, etc. by taking measures against designated substances, and by taking necessary measures for the promotion of research and development of pharmaceuticals, medical devices and regenerative medicine products which fulfill particularly high medical needs.

The same act regulates medicinal products for human use (MPs) and veterinary medicinal products (VMPs)

Article 2 [Definition]

- The term "pharmaceutical" used in this Act refers to the following items:

(i) items listed in the Japanese Pharmacopoeia;

(ii) items which are intended for use in the diagnosis, treatment or prevention of disease in humans or animals

(iii) items which are intended to affect the structure and functioning of a human or animal's body, and which are not medical appliances or instruments, etc.

PMD Act

Article 14 [Marketing Approval]

- A person who intends to market pharmaceuticals*1 , quasi-pharmaceutical products*2 or cosmetics which contain components specified by the Minister must, for each product, obtain approval from the Minister with respect to its marketing.

*1 Excluding pharmaceuticals with specified standards designated by the Minister

*2 Excluding quasi-pharmaceutical products with specified standards designated by the Minister

Composition of dossiers (Vaccines)

[Application format]

Application for Marketing Approval

1 Name and address of manufacturer(s)
2 License No. of manufacturer(s)
3 Type of License
4 Name of the product
5 Ingredients and quantities
6 Manufacturing method
7 Administration and dosage
8 Label claim
9 Condition for storage
10 Shelf life
11 Quality control testing and acceptance criterion
12 References

Composition of dossiers (Vaccines)

[Appendixes (background study data)]

Appendix 1: Origin and background of development
Appendix 2: Physicochemical properties
Appendix 3: Production protocol
Appendix 5: Stability
Appendix 9: Target Animal Safety
Appendix 10: Efficacy
Appendix 14: Clinical trial

Appendix 1

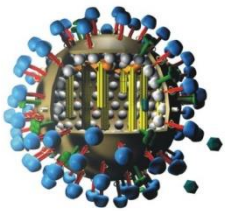
The origin and background of the development

- Purpose of development
- Information on the target disease(s)
- Information on outbreaks of the target disease(s) in Japan
- Information on the similar products approved outside Japan
- Component comparison with similar vaccines already approved in Japan

Appendix 2

Physicochemical property of vaccine strain

- Origin of the strain and seed production process
- Attenuation, strain marker and stability (live vaccine)
- Excretion and cohabitation infection (live vaccine)
- Immunogenicity
- **Absence of reversion to virulent form (VICH GL41)**
- Safety of master seed in target animal
- **Quality control testing** (seeds, in-process and batch release) and acceptance criterion (VICH GLs)

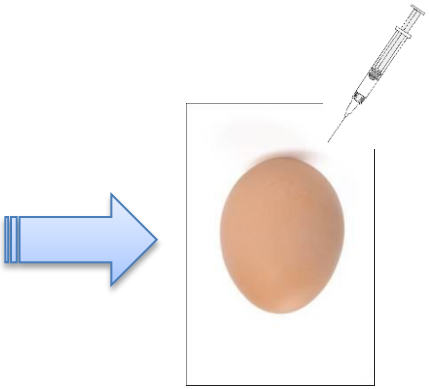


Appendix 3

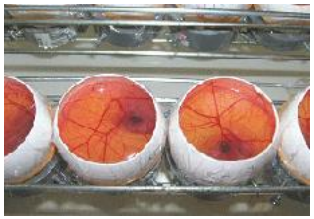
Protocol of production

Live-attenuated viral vaccine

1 Inoculate production seed virus in eggs



Incubate for XXX days at 37 ˚C



2 Harvest, filter and centrifuge virus fluid

3 Dilute and add stabilizer

4 Place aliquots in vials and freeze-dry

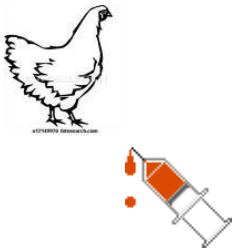
Appendix 5

Stability of Final product (Shelf life)

- Method: Long-term stability test
- Sample: Final products
- Number of sample: 3 batches
- Test interval : every 3 (6, 12) months
- Test items: All items of the final products

Appendix 9

Target animal Safety test (TAS)

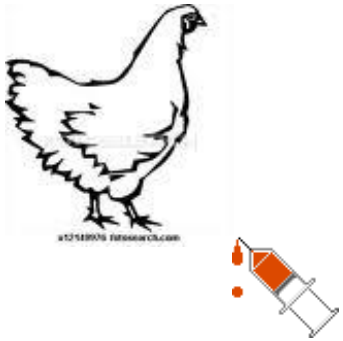


- **GLP study**
- Method: VICH GL44
- Material: final products
- Number of Animals: 8 animals in each group
- Administration dose:
  - Live vaccine given at 10 doses / animal
  - Inactivated vaccine given at 1 dose / animal
- Data Collection:
  - General clinical observations (vitality, diarrhea, respiration, body weight)
  - Injection site (histopathologically after euthanasia)

Appendix 10

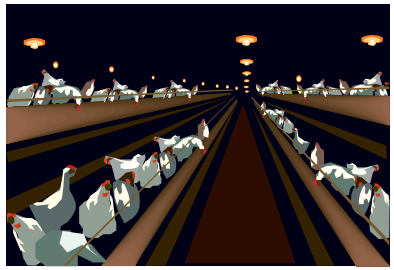
Efficacy

- Minimum effective dose
- Minimum effective antibody titer
- Comparative study on sensitivity by age, breed and administration route
- Influence of maternal antibody on vaccination
- Duration of immunity
- Onset of immunity



Appendix 14

Clinical trial



- **GCP study** (**VICH GL9**)
- Objective :
  - To evaluate the **efficacy** and **safety** of the vaccine in the field
- Samples: Final products
- Number of test sites: More than 2 sites
- Number of Animals:
  - ≥ 200 chickens
  - ≥ 60 head for mammals
- Test period:
  - Adequate period for evaluation of safety and efficacy of the vaccine in field

Composition of dossiers (Chemicals)

[Application format]

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1 Name and address of manufacturer(s)
2 License No. of manufacturer(s)
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Composition of dossiers (Chemicals)

[Appendixes (Background study data)]

App. 1: Origin and background of the discovery

App. 2: Physicochemical properties

App. 3: Production protocol

App. 5: Stability

App. 6: Toxicity (acute toxicity)

App. 7: Toxicity (sub acute and chronic toxicity)

App. 8: Toxicity (special toxicity (e.g. mutagenicity, local irritation, etc.)

* App. 4 is only for Medical Devices

Composition of dossiers (Chemicals)

[Appendixes (Background study data)]

App. 9: Target Animal Safety
App.10: Pharmacology related to efficacy
App.11: General pharmacology
App.12: ADME (absorption, distribution, metabolism and excretion)
App.14: Clinical trial
App.15: Residue for food producing animals

* App. 13 is only for Medical Devices

Appendix 5

Stability

- Active ingredient

  Guideline: VICH GL3R

  - Long term
  - Accelerated
  - Photostability (VICH GL5)

- Final product

  Guideline: VICH GL3R

  - Long term
  - Accelerated
  - Photostability (VICH GL5)

- Other GLs (VICH GL4, GL8, GL17, GL45, GL51)

Appendix 6-8

Toxicity

- General approach to testing (VICH GL33)
- Acute toxicity
- Sub acute and chronic toxicity (VICH GL31, GL37)
- Reproduction toxicity (VICH GL22)
- Developmental toxicity (VICH GL32)
- Genotoxicity (VICH GL23)
- Additional studies if needed

Appendix 10

Efficacy

- Mode of action
- Minimum effective dose
- Basis of administration route and dosage

Appendix 11

General pharmacology

Effects for

-central nervous system,

-autonomic nervous system,

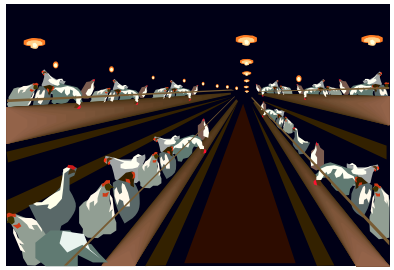
-respiratory system,

-circulatory system and

-gastrointestinal system

Appendix 14

Clinical trial



- Objective :
  - To evaluate the efficacy and safety of the final product in the field
- Samples: Final product
- Number of test sites: More than 2 sites
- Number of Animals:
  - ≥ 200 chickens
  - ≥ 60 head for mammals
- Test period:
  - Adequate period for evaluation of efficacy and safety

Appendix 15

Residue for food producing animal

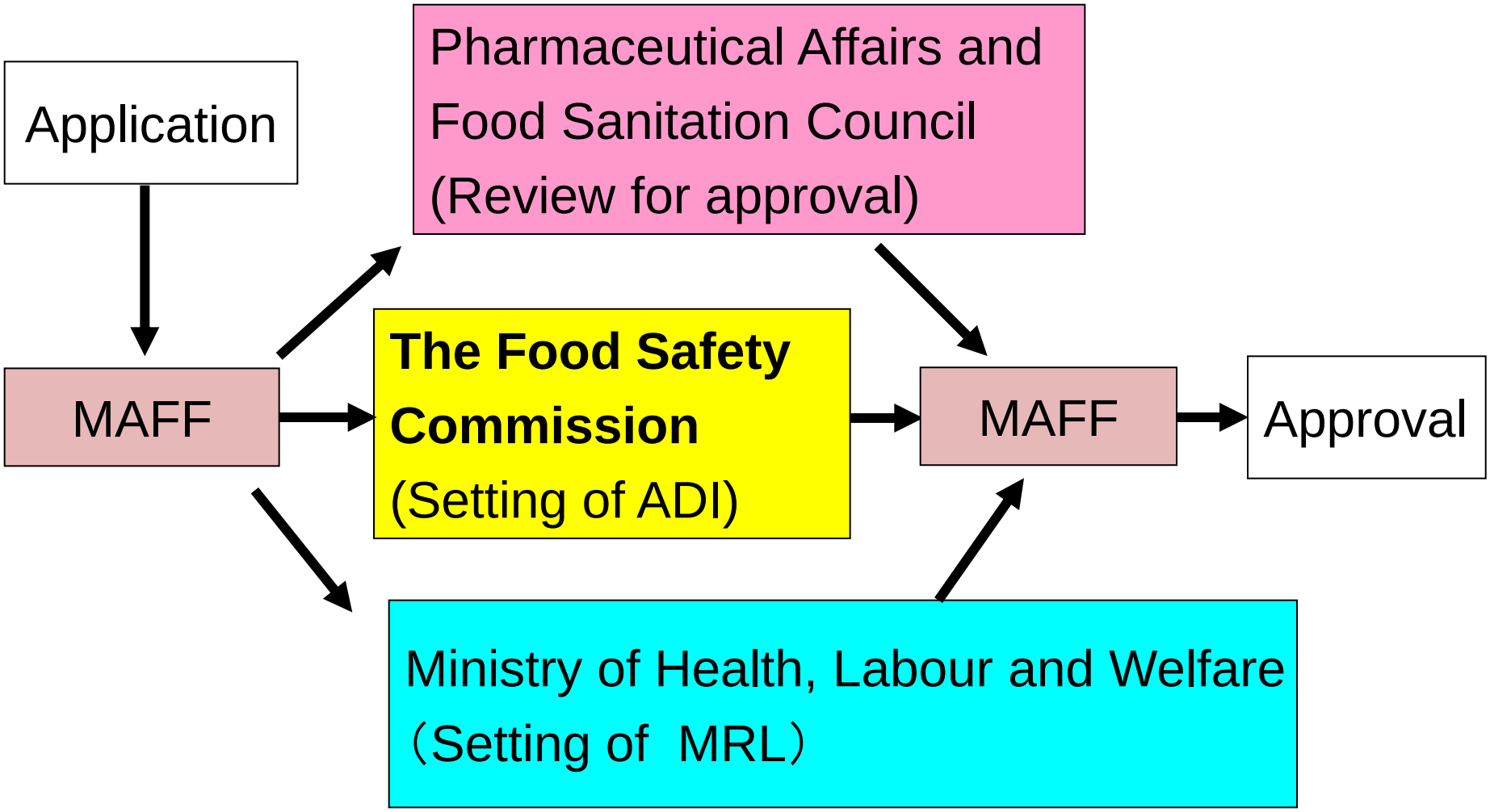
- Objective :
  - To evaluate the residue of active ingredient in the food producing animals when the veterinary drug product administrates with maximum dose and maximum period. This study will be used for establishing of MRL and withdrawal period.
- Methods: VICH GLs 46-49

Council and Commission

- Article 14, paragraph 8
  - When any one of the following items is met, the Minister shall seek the opinion of Pharmaceutical Affairs and Food Sanitation Council (PAFSC) before granting the approval specified in Paragraph 1.
    - (1) …
    - (2) …
  - The expert of veterinary medicine, pharmaceutical sciences, toxicology, bacteriology, etc.

- Drugs for food producing animals
  - drug residues
    - PAFSC
  - Human health safety
    - Food Safety Commission of Cabinet Office (FSC)

From application to approval



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Feed Additives

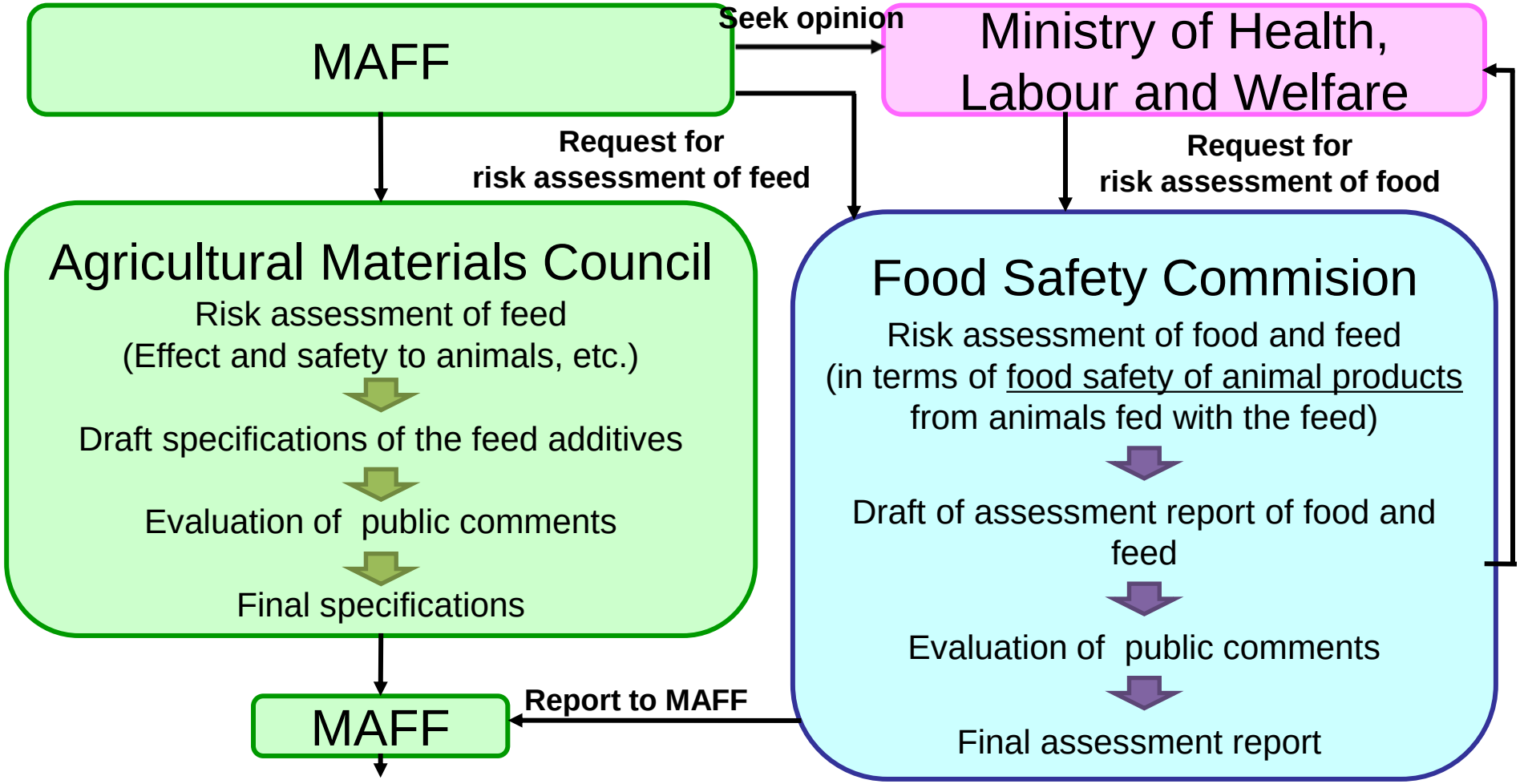
Feed additives in Feed Safety Act refer to

- those used in feeds by adding, mixing, infiltrating, etc.
- for the purpose specified by MAFF Ordinance,
- which are designated by the Minister of Agriculture, Forestry and Fisheries after consultation with the Agricultural Materials Council.

Purposes specified by MAFF Ordinance

- Prevent deterioration of feed quality
- Supply of nutrient ingredients and other effective ingredients of feed
- Promote efficient use of feed nutrient ingredients

Procedure for designating feed additives



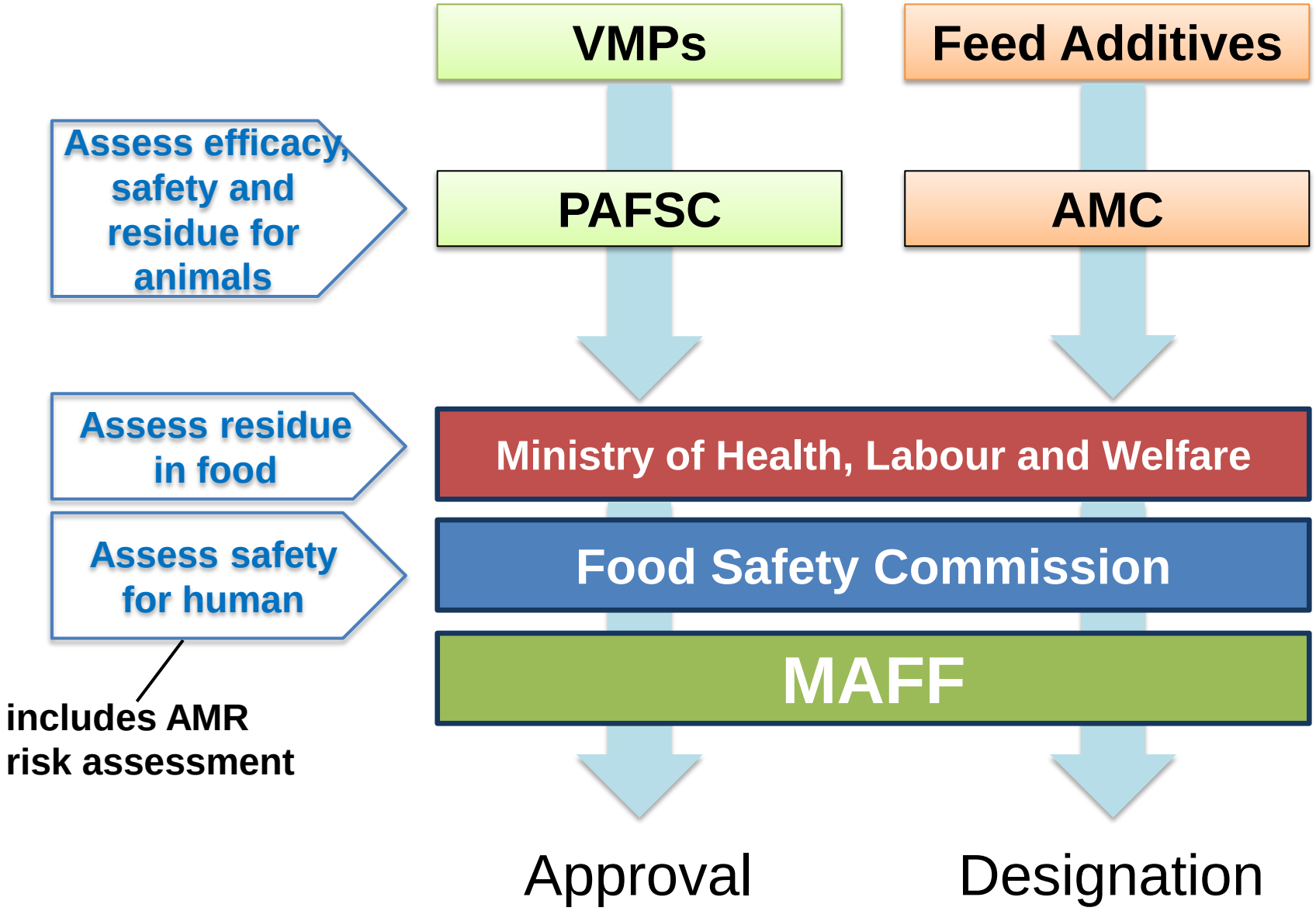
Designating the feed additives
Setting the specifications

Assessment standards for feed additives

1. Efficacy
2. Residue
3. Safety

of candidate feed additives are discussed at the Agricultural Materials Council

Approval/designation Procedure



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For the promotion of R&D

- ✓ VMPs are essential tools for comprehensive control of the animal diseases. Feed additives are important for the production of healthy animals. Our Industry highly contributes to animal health worldwide.

- ✓ Our mission as the Regulatory Authority is to provide safe and efficacious products with high quality to veterinarians, farmers and pet owners as early as possible. To achieve this, we continue to improve our approval/designation process for VMPs and feed additives.

- ✓ Japan promotes the developments of alternatives to antibiotics by financially supporting the final stage of the developments.

For the promotion of R&D

- ✓ Technical guidelines are fundamental for research & development by applicants and review by regulatory authority. Japan promotes to develop new national and international guidelines for VMPs with close relationship with Industry/Academia.

- ✓ Fast Track Approval for VMPs to be used for combatting AMR is under consideration. (Congress passed the bill on amendment of Pharmaceuticals and Medical Devices Act in November)

- ✓ To maintain communications between Regulatory authorities and Industry (as partners) is the key for the fast development and approval of the products; thus, for the future of animal and public health.

Thank you very much for your attention!!